Non-Technical Abstract.

Malignant glial tumors are uniformly very difficult to treat and are generally fatal within two years. Approximately 8000 cases are diagnosed annually in the USA. Recent progress in the use of gene therapy approaches to the treatment of cancer provides methods of treatment that can be effectively used in combination with more standard drug, surgical and radiation therapies. A two stage Phase I Clinical Safety Trial is proposed in which a guided needle will be used to directly inoculate into the brain tumor a completely inactivated herpes simplex viral gene transfer vehicle or vector referred to as NUREL-C2. NUREL-C2 contains four novel therapeutic genes referred to as HSV-infected cell protein zero (ICP0), thymidine kinase (TK), connexin 43 and tumor necrosis factor alpha (TNF-α). These genes will direct the production of four protein products within the tumor cells. Together these proteins will be highly toxic for cancer cells particularly when used in combination with intravenous administration of the anti-cancer drug ganciclovir. This treatment will spare normal brain tissue. The four therapeutic proteins will inhibit the growth and spread of the tumor cells and produce an active form of ganciclovir within tumor cells that will kill both cells "infected" by the NUREL-C2 vector as well as neighboring uninfected tumor cells. The destruction of nearby tumor cells is referred to as a bystander effect, which will be enhanced by the vector-produced proteins. Following the initial treatment, the injected tumor tissue will be surgically removed 2-4 days later and tumor tissue examined for the presence of vector, vector produced proteins and tumor cell killing. At the time of surgery, the same dose of vector will be injected into the residual tumor and ganciclovir therapy will be given intravenously. A second group of patients will be similarly injected with vector and treated with ganciclovir but additionally treated by gamma knife radiosurgery. These patients are unlikely to have surgical tumor removal. The progress of all patients will be followed by MRI and PET scanning.